

-1-

Date: 9.11.03 Express Mail Label No. EU 05 2 028 260 US

Inventors: Lijun Sun, Keizo Koya, Zhi-Qiang Xia, Teresa Przewloka,
Shijie Zhang, Mitsunori Ono

5 Attorney's Docket No.: 3211.1007-001

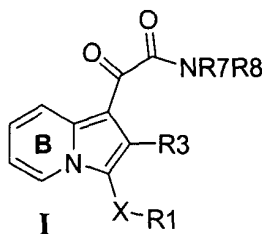
SYNTHESIS OF INDOLIZINES

RELATED APPLICATIONS

10 This application claims the benefit of U.S. Provisional Application Serial No. 60/410,679, filed September 13, 2002, the entire teachings of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

15 It has recently been disclosed in U.S. Published Application No. 20030153759 filed September 13, 2002, the entire teachings of which are incorporated herein by reference, that 1-glyoxylamide indolizines, represented by structural formula I, possess anticancer activity, even when administered individually against multi-drug resistant tumors:



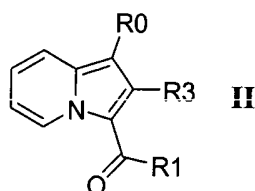
20

The variables in Formula I are defined below.

Furthermore, other substituted indolizine compounds with a range of pharmacological activity have been reported, for example, for septic shock (WO 96/03383, WO 99/51605), stroke (WO 98/47507), disorders associated with apoptosis

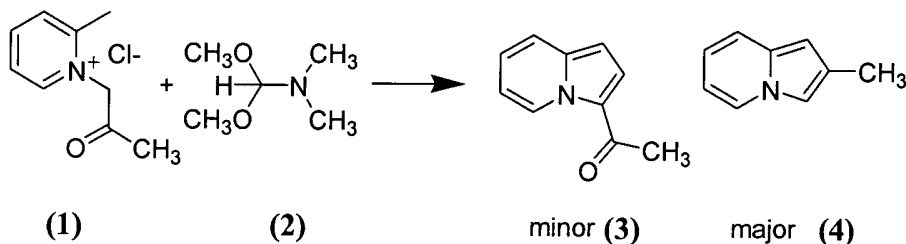
(WO99/24033), and isochemic reflow failure (WO 00/021563). There is therefore a need for new synthetic methods that efficiently produce pharmacologically active indolizines, and minimize or eliminate unwanted isomers and waste products.

3-Acyl indolizines, represented in structure **II**, are key intermediates in the preparation of many pharmacologically active indolizines, including 1-glyoxylamide indolizines:



Unfortunately, synthetic routes towards substituted indolizine intermediates in the prior art result in low overall yields of the 3-acyl isomer.

For example, Copar, A.; Stanovnik, B.; Tisler, M. *J. Heterocyclic Chem.* **30**, 1993, 1577-1579 disclose the preparation of acyl indolizines by reacting a substrate, shown below as 1-acetonyl-2-methylpyridinium chloride (**1**), with a cyclization reagent, specifically dimethyl formamide dimethyl acetal (**2**):

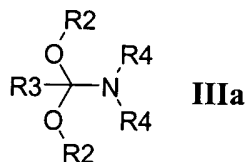


Unfortunately, in such reactions, 3-acyl indolizines are formed as minor by-products in yields ranging from 0 to 20%.

The ability to synthesize 3-acyl indolizines economically and in high yield is a prerequisite to making pharmacologically active indolizines viable as drug candidates. This is essential to bringing new medicines to the public, including anticancer compounds such as **I**. Herein is disclosed significantly improved synthesis of substituted indolizine compounds.

SUMMARY OF THE INVENTION

It has now been found that 3-acyl indolizines such as structure **II** can be prepared in high yield by the use of new, sterically hindered cyclization reagents. The surprising and significant effect of using these new cyclization reagents is that the prior art product distribution is reversed—the 3-acyl indolizine is the major cyclization product and the 2-acyl indolizine is the minor product or is not observed at all. Typically, yields of the 3-acyl indolizine are 70% or greater (see Examples 1 and 2). For example, one such cyclization reagent is represented by structure **IIIa**:

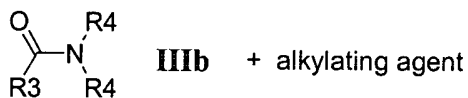


Each R2 is independently a substituted or unsubstituted aliphatic group, or a substituted or unsubstituted aryl group; or both R2 groups, taken together, are an inert linking group. When R3 is –H, R2 is preferably a secondary or tertiary alkyl group or a substituted or unsubstituted aryl group.

R3 is –H, a substituted or unsubstituted aliphatic group, a substituted or unsubstituted aryl group, or an electronegative or electropositive group. Preferably, R3 and R0 are both –H or a substituted or unsubstituted aliphatic group.

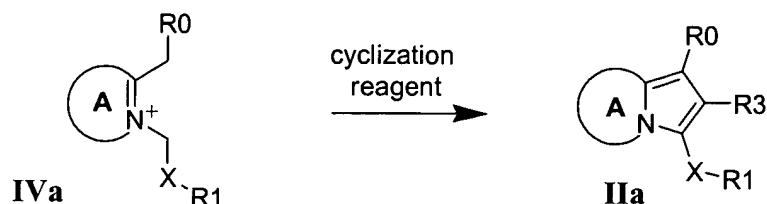
Each R4 is –H, a substituted or unsubstituted aliphatic group, a substituted or unsubstituted aryl group, or both R4 groups, taken together with the nitrogen atom to which they are bonded, are a substituted or unsubstituted heterocyclic group.

Another cyclization reagent is prepared by reacting a compound represented by structure **IIIb** with an alkylating agent.



R3 and R4 are as defined above for **IIIa**.

The present invention is directed towards a method of preparing a product compound **IIa** by reacting a substrate **IVa** with one of the cyclization reagents defined above:



Ring A is a substituted or unsubstituted heteroaryl group.

X is a covalent bond, or a linking group selected from a methanone, a sulfone, a sulfoxide, a substituted or unsubstituted amine, or a substituted or unsubstituted methylene. Preferably, X is a linking group selected from a methanone, a sulfone, a sulfoxide, or a substituted or unsubstituted methylene. More preferably, X is a methanone.

R0 is -H, a substituted or unsubstituted aliphatic group, a substituted or unsubstituted aryl group, a substituted or unsubstituted non-aromatic heterocyclic group, a halogen, -CN, -COR^a, -CO₂R^a, -CONR^aR^b, -SO₂R^a, or -SO₂NR^aR^b.

R1 is -H, a substituted or unsubstituted aliphatic group, a substituted or unsubstituted aryl group, a substituted or unsubstituted non-aromatic heterocyclic group, -CN, -OR^a, -SR^a, or -NR^aR^b.

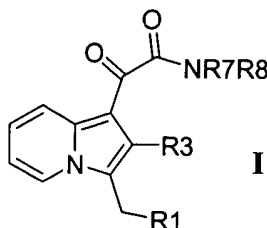
R3 is as described above for structure **IIIa**.

R^a and R^b are independently -H, alkyl, or aryl.

The advantages of the invention disclosed herein are significant. The improvements in the yield of the key cyclization step allow pharmacologically active indolizines, including the anticancer drugs disclosed in U.S. Provisional Application No. 60/322,020, to be made economically in pharmaceutically useful quantities. Furthermore, because this key step occurs early in the overall synthetic path, it enables the preparation of a wide range of structural variants that can be used in screening assays for other therapeutic targets. Finally, the higher yield and concomitant lack of byproduct formation leads to less waste, and thus an environmentally responsible process.

DETAILED DESCRIPTION OF THE INVENTION

The methods disclosed herein can be used to prepare derivatives of nitrogen-containing polyaromatic systems, including indolizines, and in particular 3-acyl indolizines. The term indolizine refers to the two fused rings in structure **I**:



5 The method comprises the step of preparing a compound of structure **IIa** by a cyclization or ring forming reaction between the cyclization reagent and a substrate of structure **IVa**. One such cyclization reagent is **IIIa**. The other cyclization reagent is prepared by reacting **IIIb** with an alkylating agent. The variables in **IIIa** and **IIIb** are defined in the summary.

The cyclization reagent **IIIa**, in a molar ratio of 0.75 to 100 is combined with the substrate in a polar solvent and reacted at 70-170°. The polar solvent can be a polar protic solvent, such as water or an alcohol; a polar aprotic aromatic solvent such as nitrobenzene; or a polar aprotic solvent such as nitromethane, dimethyl acetamide (DMA), N,N-dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), hexamethyl phosphoramide (HMPA), N-methyl pyrrolidone (NMP), tetrahydrofuran (THF), or dioxane.

Alternatively, cyclization reagent **IIIa**, in a molar ratio of 0.75 to 100 is combined with the substrate in a polar solvent and reacted, the latter suspended or dissolved in a polar organic solvent such as an alcohol, nitrobenzene, nitromethane, DMA, DMF, DMSO, HMPA, NMP, THF, or dioxane. The resulting mixture is heated to between 100 to 160° C.

Preferably, cyclization reagent **IIIa**, in a molar excess of 5 to 15, is combined with the substrate in a solvent selected from DMA, DMF, DMSO, HMPA, NMP, nitrobenzene, nitromethane, or THF. The resulting mixture is heated to between 120 to 160° C.

Details of a specific preparation can be found in Example 2.

The cyclization reagent **IIIb**, in a molar excess of 2 to 100, and an alkylating agent, in a molar ratio of between 2 to 100, and the substrate, in a molar ratio of 1, are combined with a polar solvent and reacted at 25° to 70°C. The polar solvent can be a
5 polar protic solvent, such as water or an alcohol; a polar aprotic aromatic solvent such as nitrobenzene; or a polar aprotic solvent such as nitromethane, DMA, DMF, DMSO, HMPA, NMP, THF, or dioxane, provided that said solvent is not a formamide different from **IIIb**. Subsequently, an excess of an amine is added and the mixture is stirred at 25 to 50°C.

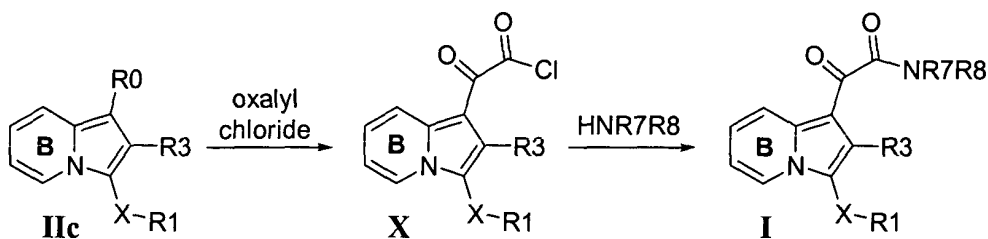
10 Alternatively, the cyclization reagent **IIIb**, in a molar excess of between 2 to 20, is combined with an alkylating agent, in a molar excess of between 2 to 20, in a polar organic solvent, and stirred for 1 to 10 h at 30 to 70°C. The polar solvent can be an alcohol, nitrobenzene, nitromethane, DMA, DMF, DMSO, HMPA, NMP, THF, or dioxane, provided that said solvent is not a formamide different from **IIIb**. The result is
15 combined with a solution of the substrate in said solvent, in a molar ratio of 1, and the mixture is reacted at 30 to 50° C. Subsequently, an excess of a trialkyl amine is added and the mixture is stirred at 30 to 50° C.

Preferably, the cyclization reagent **IIIb**, in a molar excess of 6 to 12, is combined with an alkylating agent, in a molar excess of between 6 to 12, in a polar
20 organic solvent selected from the group of DMA, DMF, DMSO, HMPA, NMP, nitrobenzene, nitromethane, or THF, and reacted at 30 to 70°C, provided that said solvent is not a formamide different from **IIIb**. The result is combined with a solution of the substrate in said solvent, in a molar ratio of 1, and the mixture is reacted at 30 to 50° for between 45 to 75 minutes. Subsequently, an excess of triethyl amine is added
25 and the mixture is stirred at 35 to 45° C.

Details of a specific preparation can be found in Example 1.

As noted previously, substituted indolizines prepared as detailed above can serve as starting materials for synthesizing 1-glyoxylamide indolizine such as **I**.
Compounds represented by structure **X** can be prepared from compounds represented

by structure **IIc** by acylation with, for example, oxalyl chloride or a synthetic equivalent thereof (e.g., oxalyl bromide):



In the above scheme, R_0 and R_3 are $-H$ and X , R_7 , R_8 and Ring **B** are as described previously. Although equimolar amounts of an intermediates such as **IIc** and acylating agents can be used, typically the acylating agent is used in excess, for example, up to a twenty fold molar excess, preferably up to a ten fold molar excess and more preferably up to a three fold molar excess. Ethereal solvents (e.g., diethyl ether, tetrahydrofuran, 1,4-dioxane, glyme, diglyme and methyl *tert*-butyl ethyl) and aromatic solvents (e.g., benzene, toluene and xylene) are commonly used. Suitable reaction temperatures range from -50°C to the boiling point of the solvent and more typically range from -10°C to room temperature and preferably between -10°C to 10°C . Detail of specific examples of this reaction are provided in U.S. Provisional Application No. 60/322,020, filed September 13, 2001.

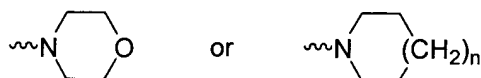
Compounds represented by structure **X** are converted into structure **I** by reacting the acylated intermediate with amine HNR_7R_8 , wherein R_7 and R_8 are as described above. The acylated intermediate and the amine are mixed in a suitable solvent, e.g., an ethereal solvent or aromatic solvent. Suitable reaction temperatures are as described above for the acylation reaction. Although an excess of one reactant can be used (e.g., up to a ten-fold molar excess), more typically, between a 20% molar and 100% molar excess is used. When less than two equivalents of amine HNR_1R_2 are used, a tertiary amine such as triethylamine or dimethylaminopyridine is generally added so that at least two equivalents of amine compared to the acylated intermediate are present in the reaction mixture. Specific examples of this reaction are provided in U.S. Provisional Application No. 60/322,020, filed September 13, 2001.

In a preferred embodiment, the variables in **IIIa** and **IIIb** are defined in the following paragraphs.

Each R² is a substituted or unsubstituted cyclic aliphatic group, or -CH(R^c)₂ or -C(R^c)₃, and each R^c is independently a C1-C4 alkyl group. Preferably each R² is independently -CH(CH₃)₂, -C(CH₃)₃, cyclobutyl, 2,2',4,4'-tetramethylcyclobutyl, cyclopentyl, 2,2',5,5'-tetramethylcyclopentyl, cyclohexyl, 2,2',6,6'-tetramethylcyclohexyl, phenyl, or 2,6-dimethylphenyl.

R³ is as described above for structure **IIIa**. Preferably, R³ is -H, methyl, ethyl, or propyl. More preferably, R³ is -H.

Each R⁴ is -H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂ or -C(CH₃)₃. Alternatively, both R⁴ groups, taken together with the nitrogen atom to which they are bonded, are a cyclic group as shown below:



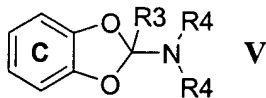
n is 0, 1, or 2.

In another preferred embodiment, the variables in **IIIa** and **IIIb** are defined in the following paragraphs.

Both R² groups, taken together, are -(CR⁵)_n-, each R⁵ is independently -H or -CH₃, and n is 1, 2, or 3.

R³ and R⁴ are as described above for structure **IIIa**. Preferably, R³ is -H, methyl, ethyl, or propyl, and R⁴ is methyl, ethyl or propyl. More preferably, R³ is -H.

In yet another preferred embodiment, the cyclization reagent represented by **IIIa** is represented by **V**:

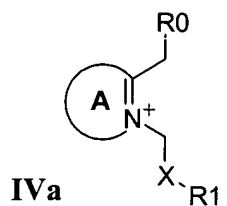


R³ and R⁴ are as described for structure **IIIa**. Preferably, R³ is -H, methyl, ethyl, or propyl, and R⁴ is methyl, ethyl or propyl. More preferably, R³ is -H.

Ring **C** is unsubstituted or substituted. More preferably, ring **C** is unsubstituted.

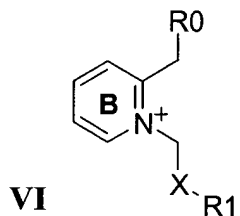
Most preferably, the cyclization reagent is *N,N*-dimethylformamide-di-*tert*-butyl acetal, *N,N*-dimethylacetamide-di-*tert*-butyl acetal, *N,N*-dimethylbenzamide-di-*tert*-butyl acetal, *N,N*-dimethylpropamide-di-*tert*-butyl acetal, or *N,N*-dimethyl-2-propamide-di-*tert*-butyl acetal; or is prepared by reacting *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N,N*-dimethylbenzamide, *N,N*-dimethylpropamide, or *N,N*-dimethyl-2-propamide with an alkylating agent.

The substrate used in the disclosed cyclization reaction is represented by structure **IVa**.

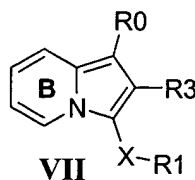


The reaction of a substrate of structure **IVa** with one of cyclization reagents disclosed herein results in the formation of a product of structure **IIa**. The variables in structures **IIIa**, **IIIb** and **IVa** are defined above. Preferably, *R*0 and *R*3 are both -H or a substituted or unsubstituted aliphatic group.

Preferably, the substrate is represented by structure **VI**:



The reaction of a substrate of structure **VI** with one of the cyclization reagents disclosed herein results in the formation of a product represented by structure **VII**:



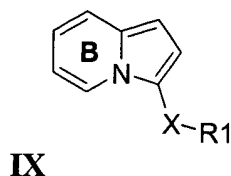
*R*0, *R*1, *R*3 and *X* in structures **VI** and **VII** are as described in structure **IVa**; and Ring **B** is substituted or unsubstituted. Suitable substituents for Ring **B** include those described below as being aryl ring substituents. Preferred substituents for Ring **B**

include one or more groups selected from $-F$, $-Cl$, $-Br$, C1-C4 alkyl, C1-C4 alkoxy, $-C1-C4$ haloalkyl, C1-C4 haloalkoxy, $-NH_2$, $-NO_2$, or $-CN$. Preferably, however, Ring **B** is unsubstituted.

In a preferred embodiment, the substrate is represented by formula **VIII**:



and R3 in the cyclization reagent is $-H$, resulting in the formation of a product represented by structure **IX**:

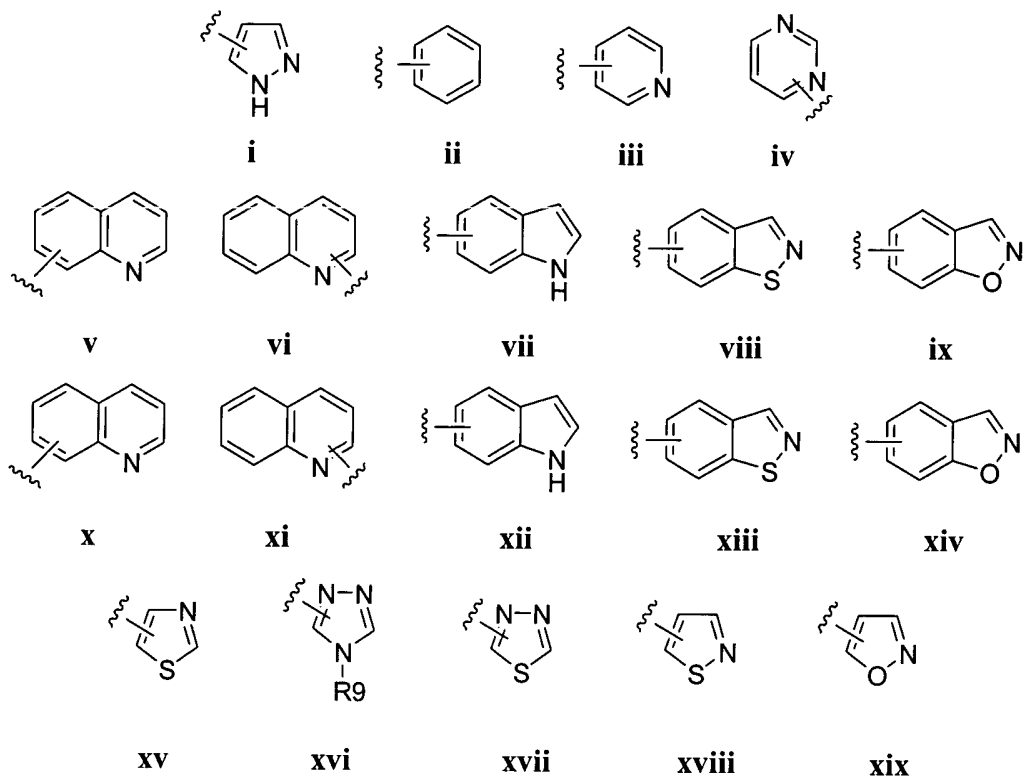


The variables in structure **VIII** and **IX** are as defined in structures **VI** and **VII**.

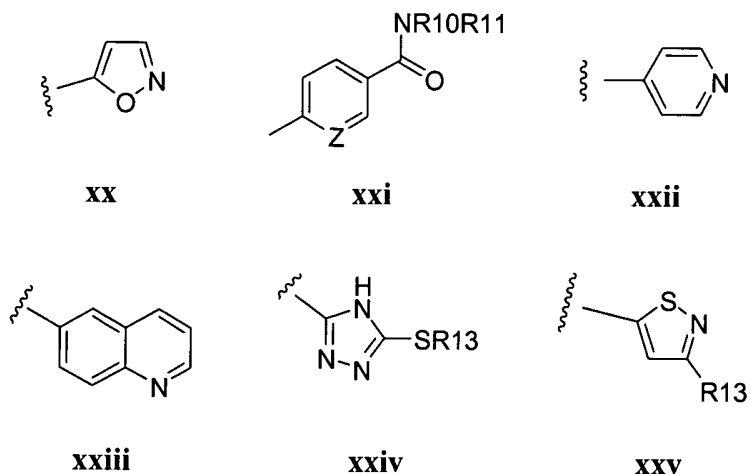
- 10 Preferably, R1 is an optionally substituted phenyl, pyridyl, furanyl, thienyl, pyrazolyl, or pyrrolyl group (preferably phenyl group). Suitable substituents those described below as being aryl ring substituents. Preferably, the phenyl, pyridyl, furanyl, thienyl, pyrazolyl, or pyrrolyl group represented by R1 is substituted with zero, one or more substituents selected from $-Br$, $-Cl$, $-F$, $-R^a$, $-OR^a$, $-CN$, $-COOR^a$, $-N(R^a)_2$,
 15 $-CON(R^a)_2$, $-NR^aCOR^b$, $-NHCONH_2$, or $-SO_2N(R^a)_2$; and R^a and R^b are independently $-H$, an alkyl group or a substituted alkyl group. Especially preferred substituents for a phenyl ring represented by R1 are $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-CN$, $-F$ and $-Cl$, which are preferably at the *para* position relative to the methanone.

- In structure **I**, variables X, R1 and R3 are as described for structure **IVa**; ring **B**
 20 is as defined for structure **VI**; and R7 and R8 are independently $-H$, a substituted or unsubstituted aliphatic group, a substituted or unsubstituted non-aromatic heterocyclic group, or a substituted or unsubstituted aryl group, provided that R7 or R8 are not both $-H$. Alternatively, NHR_7R_8 , taken together, is a substituted or unsubstituted non-aromatic heterocyclic group, or a substituted or unsubstituted aryl group.

- Preferably in structure **I**, X, R1 and R3 are as described for structure **IVa**; ring **B** is as defined for structure **VI**; R7 is -H; and R8 is a substituted or unsubstituted aliphatic group or a substituted or unsubstituted aryl group. Suitable values for R8 are in the section defining aryl groups. Commonly used aryl groups for R8 are selected
- 5 from structural formulas **i-xix** below:



- 10 R9 is -H or a substituted or unsubstituted alkyl group. A more preferred value for R8 is a substituted or unsubstituted aryl group selected from structural formulas **xx-xxv**:



Z is –CH– or –N–; R10 and R11 are independently –H or an alkyl group, or –NR10N11 taken together is a non-aromatic heterocyclic group; R12 is an alkyl group; and R13 is –H or an alkyl group. Structure xxv is a more preferred valued for R8 wherein R13 is –H, or a substituted or unsubstituted aliphatic group and preferably –CH₃.

5 An alkylating agent is a compound comprising an electrophilic alkyl group and a leaving group. Such agents are well-known to practitioners of the art. Examples include dialkyl sulfate or an alkyl mesylate, tosylate, triflate, chloride, bromide, or iodide. Preferably, the alkylating agent is dimethyl sulfate.

 An inert linking group is any group that connects two other groups and does not
10 substantially interfere with the reactions described herein. “Interfering with a reaction” refers to substantially decreasing the yield (e.g., a decrease of greater than 50%) or causing a substantial amount of by-product formation (e.g., where by-products represent at least 50% of the theoretical yield). Interfering substituents can be used, provided that they are first converted to a protected form. Suitable protecting groups are known in the
15 art and are disclosed, for example, in Greene and Wuts, "Protective Groups in Organic Synthesis", John Wiley & Sons (1991).

 An aliphatic group is a straight chained, branched or cyclic (non-aromatic) hydrocarbon which is completely saturated or which contains one or more units of unsaturation. Typically, a straight chained or branched aliphatic group has from one to
20 about twenty carbon atoms, preferably from one to about ten, and a cyclic aliphatic group has from three to about eight ring carbon atoms. An aliphatic group is preferably a completely saturated, straight-chained or branched alkyl group, e.g., methyl, ethyl, *n*-propyl, 2-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, pentyl or octyl, or a cycloalkyl group with three to about eight ring carbon atoms. C1-C20 straight chained
25 and branched alkyl groups and C3-C8 cycloalkyl groups are also referred to herein as “lower alkyl groups”. Aliphatic groups may additionally be substituted or be interrupted by another group.

 Aryl groups include carbocyclic aromatic groups such as phenyl, naphthyl, and anthracyl, and heteroaryl groups such as imidazolyl, isoimidazolyl, thienyl, furanyl,

pyridyl, pyrimidyl, pyranyl, pyrrolyl, pyrazolyl, pyrazinyl, thiazolyl, isothiazolyl, oxazolyl, isooxazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, and tetrazolyl.

Aryl groups also include fused polycyclic aromatic ring systems in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other heteroaryl
 5 rings. Examples include benzothienyl, benzofuranyl, indolyl, isoindolyl, quinolinyl, benzothiazolyl, benzoisothiazolyl, benzooxazolyl, benzoisooxazolyl, benzimidazolyl, indoliziny, quinolinyl, and isoquinolinyl.

Non-aromatic heterocyclic rings are non-aromatic carbocyclic rings that include one or more heteroatoms such as nitrogen, oxygen or sulfur in the ring. The ring
 10 can be from three to about eight ring atoms. Examples include epoxyl, oxazolinyl, oxazolidinyl, thiazolinyl, thiazolidinyl, tetrahydrofuranyl, tetrahyrothienyl, morpholino, thiomorpholino, pyrrolidinyl, piperazinyl, and piperidinyl.

Suitable substituents on alkyl, aliphatic, aryl, or non-aromatic heterocyclic groups are those that do not substantially interfere with the reactions described herein.
 15 "Interfering with a reaction" refers to substantially decreasing the yield (e.g., a decrease of greater than 50%) or causing a substantial amount of by-product formation (e.g., where by-products represent at least 50% of the theoretical yield). Interfering substituents can be used, provided that they are first converted to a protected form. Suitable protecting groups are known in the art and are disclosed, for example, in
 20 Greene and Wuts, *ibid*. Suitable substituents on an alkyl, aliphatic, aryl, or non-aromatic heterocyclic groups include, for example, -OH, halogen (-Br, -Cl, -I and -F), -OR^d, -O-COR^d, -COR^d, -CN, -NO₂, -COOH, -SO₃H, -NH₂, -NHR^d, -N(R^dR^e), -COOR^d, -CHO, -CONH₂, -CONHR^d, -CON(R^dR^e), -NHCOR^d, -NRCOR^d, -NHCONH₂, -NHCONR^dH, -NHCON(R^dR^e), -NR^fCONH₂, -NR^fCONR^dH, -NR^fCON(R^dR^e),
 25 -C(=NH)-NH₂, -C(=NH)-NHR^d, -C(=NH)-N(R^dR^e), -C(=NR^f)-NH₂, -C(=NR^f)-NHR^d, -C(=NR^f)-N(R^dR^e), -NH-C(=NH)-NH₂, -NH-C(=NH)-NHR^d, -NH-C(=NH)-N(R^dR^e), -NH-C(=NR^f)-NH₂, -NH-C(=NR^f)-NHR^d, -NH-C(=NR^f)-N(R^dR^e), -NR^gH-C(=NH)-NH₂, -NR^g-C(=NH)-NHR^d, -NR^g-C(=NH)-N(R^dR^e), -NR^g-C(=NR^f)-NH₂, -NR^g-C(=NR^f)-NHR^d, -NR^g-C(=NR^f)-N(R^dR^e), -NHNH₂, -SO₂NH₂, -SO₂NHR^d,
 30 -SO₂NR^dR^e, -CH=CHR^d, -CH=CR^dR^e, -CR^f=CR^dR^e, -CR^f=CHR^d, -CR^f=CR^dR^e,

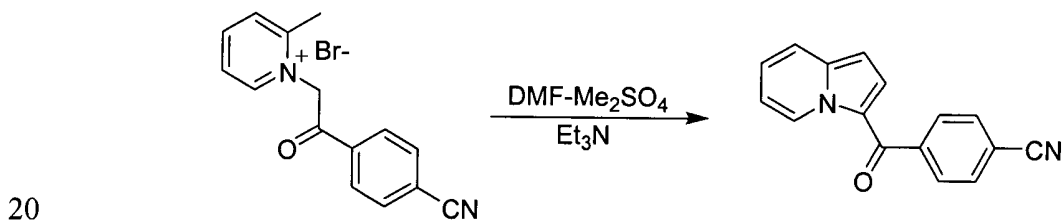
- CCR^d, -SH, -SO_kR^d (k is 0, 1 or 2) and -NH-C(=NH)-NH₂. R^d-R^g each are independently an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group, preferably an alkyl, benzylic or aryl group. In addition, -NR^dR^g, taken together, can also form a substituted or unsubstituted non-aromatic heterocyclic group. A benzylic group, non-aromatic heterocyclic group or aryl group can also have an aliphatic or substituted aliphatic group as a substituent. A substituted alkyl or aliphatic group can also have a non-aromatic heterocyclic ring, a substituted non-aromatic heterocyclic ring, benzyl, substituted benzyl, aryl or substituted aryl group as a substituent. A substituted aliphatic, non-aromatic heterocyclic group, substituted aryl, or substituted benzyl group can have more than one substituent.

Pharmacologically active indolizines disclosed elsewhere (WO 96/03383, WO 99/51605, WO 98/47507, WO99/24033, and WO 00/021563) can also be prepared by combining the present invention with a suitable choice of starting materials.

15 EXEMPLIFICATION

The present invention is illustrated by the following examples, which are not intended to be limiting in any way.

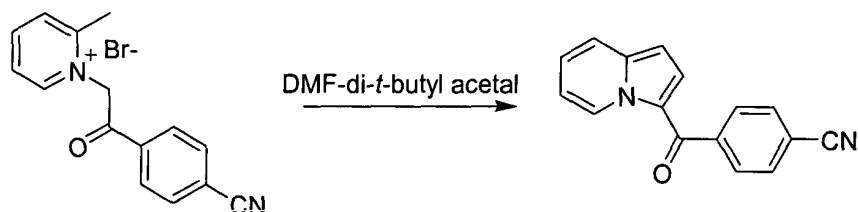
Example 1: New cyclization gives high yield of indolizine intermediate and reduced byproducts: 4-(Indolizine-3-carbonyl)-benzonitrile



- To 2-methyl-1-(4-cyano)-phenacyl pyridinium bromide (50g, 120 mmol) DMF (500 mL) suspension solution was added DMF-Me₂SO₄ (400 mL, the mixture obtained by stirring a mixture of 1 eq. DMF and 1eq Me₂SO₄ at 60°C for 3h, then allowing to rise to rt), and stirred at rt for 15 min. Subsequently, Et₃N (700 mL) was added and the mixture was stirred for 1 hr at ~ 40°C. The mixture was then added to ice water (1200 mL), and the precipitate was collected, washed with water, and dried, to give 4-

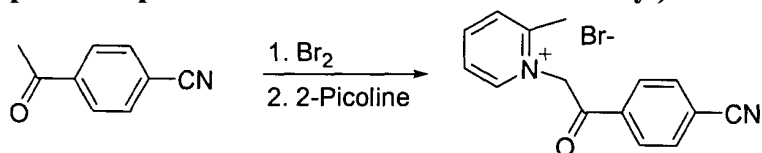
(indolizine-3-carbonyl)-benzonitrile (29 g, yield 76%). ^1H NMR (300MHz, CDCl_3): 9.95 (d, 1H), 7.87-7.75(m, 4H), 7.57(d, 1H), 7.30-7.22(m, 2H), 6.97(m, 1H), 6.55(d, 1H); ESMS calcd for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}$: 246.08; Found: 247.1 ($\text{M}+\text{H}$) $^+$.

Example 2: New cyclization gives high yield of indolizine intermediate and no significant byproducts: 4-(Indolizine-3-carbonyl)-benzonitrile



To 2-methyl-1-(4-cyano)-phenacylpyridinium bromide (5g , 12.2 mmol) DMF (50 mL) suspension solution was added N,N-dimethylformamide di-*t*-butyl acetal (30 mL) at rt. The resulting clear solution was stirred at 130°C for 4 min., then cooled to rt with an ice-water bath. Subsequently, water (100 mL) was added and the precipitate was collected and washed with water. Drying on a vacuum line gave 4-(indolizine-3-carbonyl)-benzonitrile (3.9 g, 90%) with 91% purity, which was crystallized with CH_3CN (35 mL) (82 °C to 0 °C) to give pure 2 (3.2 g). ^1H NMR (300MHz, CDCl_3): 9.95 (d, 1H), 7.87-7.75(m, 4H), 7.57(d, 1H), 7.30-7.22(m, 2H), 6.97(m, 1H), 6.55(d, 1H); ESMS calcd for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}$: 246.08; Found: 247.1 ($\text{M}+\text{H}$) $^+$.

Example 3: Preparation of a substrate: 4-indolizin-3-yl)-benzonitrile



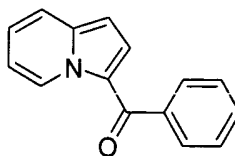
To 4-acetylbzenonitrile (14.5 g , 100 mmol) EtOAc (150 ml) solution was added Br_2 (5.1 ml, 100 mmol) at room temperature. The resulting mixture was stirred for 0.5 hr, and the solvent was evaporated under reduced pressure. The residue was dissolved in CH_3CN (100 ml), and picoline (20 ml, 200 mmol) was added to the mixture, which was then stirred for 30 minutes at room temperature and another 1 hr at 0°C. EtOAc (20 ml) was added to the mixture and the resulting precipitate was collected by filtration and washed with EtOAc to give pure 2-methyl-1-(4-cyno)-phenacylpyridinium bromide

(20.3g, 83%). ^1H NMR (300MHz, DMSO): 9.05-8.03(m, 8H), 6.78(s, 2H), 2.74(s, 3H).

PREPARATION OF OTHER COMPOUNDS:

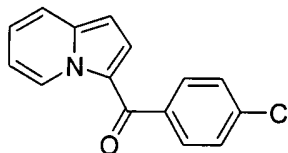
The following compounds were prepared in 75% yield or greater, except as noted, using the methods of Examples 1 and 2. Analytical data and structural formulas are provided.

Example 4: Indolizine-3-yl-phenyl-methanone



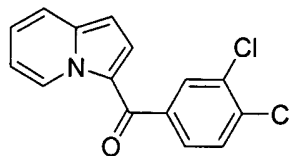
^1H -NMR (CDCl_3) δ (ppm), 9.98(d, $J=6.9\text{Hz}$, 1H), 7.80(d, $J=7.2\text{Hz}$, 2H), 7.59-7.45(m, 4H), 7.35(d, $J=4.8\text{Hz}$, 1H), 7.21(t, $J=6.9\text{Hz}$, 1H), 6.95(t, $J=6.6\text{Hz}$, 1H), 6.53(d, $J=4.8\text{Hz}$, 1H); ESMS calcd for $\text{C}_{15}\text{H}_{11}\text{NO}$: 221.08; Found: 222.1 ($\text{M}+\text{H}$) $^+$.

Example 5: (4-Chloro-phenyl)-indolizin-3-yl-methanone

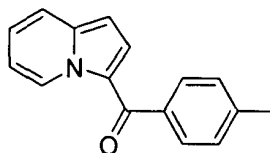


^1H -NMR (CDCl_3) δ (ppm), 9.94(d, $J=7.2\text{Hz}$, 1H), 7.75(d, $J=8.4\text{Hz}$, 2H), 7.57(d, $J=9.0\text{Hz}$, 1H), 7.46(d, $J=8.4\text{Hz}$, 2H), 7.30(d, $J=4.5\text{Hz}$, 1H), 7.21(t, $J=7.2\text{Hz}$, 1H), 6.95(t, $J=6.9\text{Hz}$, 1H), 6.53(d, $J=4.5\text{Hz}$, 1H); ESMS calcd for $\text{C}_{15}\text{H}_{10}\text{ClNO}$: 255.05; Found: 256.0 ($\text{M}+\text{H}$) $^+$.

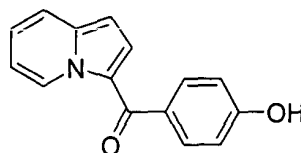
Example 6: (3,4-Dichloro-phenyl)-indolizin-3-yl-methanone



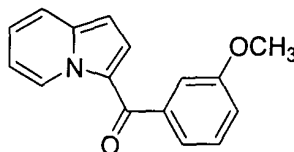
^1H -NMR (CDCl_3) δ (ppm), 9.94(d, $J=7.2\text{Hz}$, 1H), 7.89(d, $J=2.1\text{Hz}$, 1H), 7.65-7.55(m, 3H), 7.31(d, $J=4.5\text{Hz}$, 1H), 7.27-7.21(m, 1H), 6.98(t, $J=7.2\text{Hz}$, 1H), 6.56(d, $J=4.8\text{Hz}$, 1H); ESMS calcd for $\text{C}_{15}\text{H}_9\text{Cl}_2\text{NO}$: 290.14; Found: 291.1 ($\text{M}+\text{H}$) $^+$.

Example 7: Indolizin-3-yl-p-tolyl-methanone

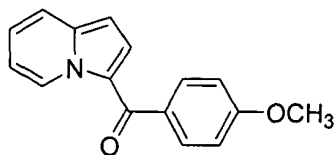
¹H-NMR (CDCl₃) δ (ppm), 9.92 (d, *J*=7.2, 1H), 7.71 (d, *J*=7.8, 2H), 7.43 (d, *J*=8.2, 1H), 7.32 (d, *J*=4.8, 1H), 7.24 (d, *J*=7.8, 2H), 7.08 (t, *J*=6.9, 1H), 6.81 (t, *J*=6.9, 1H), 6.42 (d, *J*=4.8, 1H). ESMS calcd for C₁₆H₁₁NO: 235.10; Found: 236.1 (M+H)⁺.

Example 8: 4-Hydroxyphenyl-indolizin-3-yl-methanone

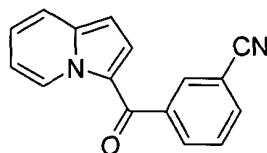
¹H-NMR (CDCl₃) δ (ppm), 9.83 (d, *J*=7.2, 1H), 7.74 (d, *J*=7.8, 2H), 7.59 (d, *J*=8.2, 1H), 7.40 (d, *J*=4.7, 1H), 7.19 (t, *J*=6.9, 2H), 6.97-6.87 (m, 3H), 6.81 (t, *J*=6.9, 1H), 6.55 (d, *J*=4.7, 1H). ESMS calcd for C₁₅H₁₁NO₂: 237.08; Found: 238.1 (M+H)⁺.

Example 9: Indolizin-3-yl-(3-methoxy-phenyl)-methanone

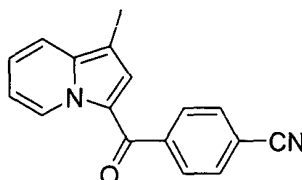
¹H-NMR (CDCl₃) δ (ppm), 9.96(d, *J*=7.2Hz,1H),7.54 (d, *J*=7.5Hz, 1H), 7.39-7.33(m, 4H), 7.16(t, *J*=6.6Hz, 1H), 7.08-7.04(m, 1H), 6.91(t, *J*=6.9Hz, 1H), 6.50(d, *J*=4.5Hz, 1H),3.85(s, 3H); ESMS calcd for C₁₆H₁₃NO₂ : 251.09; Found: 252.1 (M+H)⁺.

Example 10: Indolizin-3-yl-(4-methoxy-phenyl)-methanone

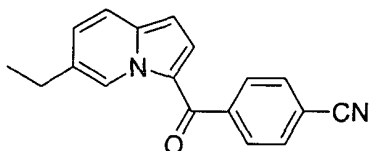
¹H-NMR (CDCl₃) δ (ppm), 9.9(d, *J*=6.9Hz, 1H), 7.84-7.80(m, 2H), 7.53(d, *J*=9.0Hz, 1H), 7.35(d, *J*=6.0Hz, 1H), 7.13(t, *J*=8.1Hz, 1H), 7.0-6.96(m, 2H),6.88(t, *J*=6.9Hz, 1H), 6.51(d, *J*=4.5Hz, 1H), 3.87(s, 3H); ESMS calcd for C₁₆H₁₃NO₂ : 251.09; Found: 252.1 (M+H)⁺.

Example 11: 3-(Indolizine-3-carbonyl)-benzonitrile

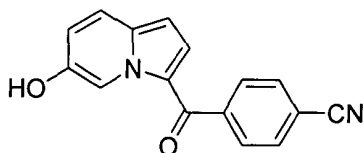
$^1\text{H-NMR}$ (CDCl_3) δ (ppm), 9.95(d, $J=7.2\text{Hz}$, 1H), 8.08-8.01(m, 2H), 7.81(d, $J=7.8\text{Hz}$, 1H), 7.64-7.59(m, 2H), 7.29-7.24(m, 2H), 7.00(t, $J=6.9\text{Hz}$, 1H), 6.57(d, $J=4.8\text{Hz}$, 1H);
 5 ESMS calcd for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}$: 246.08; Found: 247.1 ($\text{M}+\text{H}$) $^+$.

Example 12: 4-(1-Methyl-indolizine-3-carbonyl)-benzonitrile

$^1\text{H-NMR}$ (CDCl_3) δ (ppm), 9.96(d, $J=7.2\text{ Hz}$, 1H), 7.87-7.84(m, 2H), 7.79-7.76(m, 2H), 7.55(d, $J=8.7\text{ Hz}$, 1H), 7.27(t, $J=6.0\text{ Hz}$, 1H), 7.05(s, 1H), 6.99(t, $J=6.9\text{ Hz}$, 1H), 2.34(s, 3H); ESMS calcd for $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}$: 260.09; Found: 261.1 ($\text{M}+\text{H}$) $^+$.
 10

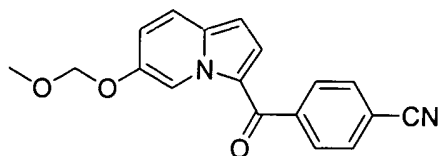
Example 13: 4-(6-Ethyl-indolizine-3-carbonyl)-benzonitrile

$^1\text{H-NMR}$ (CDCl_3) δ (ppm), 9.84(d, $J=0.9\text{Hz}$, 1H), 7.88-7.85(m, 2H), 7.79-7.76(m, 2H), 7.53(d, $J=9.0\text{Hz}$, 1H), 7.19-7.16(m, 2H), 6.5(d, $J=5.1\text{Hz}$, 1H), 2.74(q, $J=7.8\text{Hz}$, $J=15.3\text{Hz}$, 2H), 1.33(t, $J=7.2\text{Hz}$, 3H); ESMS calcd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}$: 274.11; Found: 275.1 ($\text{M}+\text{H}$) $^+$.
 15

Example 14: 4-(6-Hydroxy-indolizine-3-carbonyl)-benzonitrile

¹H-NMR (DMSO-d₆) δ (ppm), 9.94(s, 1H), 9.64(s, 1H), 8.00-7.98(m, 2H), 7.88-7.84(m, 2H), 7.73-7.69(m, 1H), 7.15-7.11(m, 2H), 6.61(d, *J*=4.8Hz, 1H); ESMS calcd for C₁₆H₁₀N₂O₂: 262.07; Found: 263.1 (M+H)⁺.

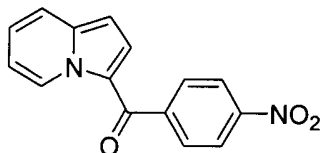
Example 15: 4-(6-Methoxymethoxy-indolizine-3-carbonyl)-benzonitrile



5

¹H-NMR (CDCl₃) δ (ppm), 9.92((s, 1H), 7.87(d, *J*=8.1Hz, 2H), 7.77(d, *J*=8.1Hz, 2H), 7.52(d, *J*=9.3Hz, 1H), 7.19-7.14(m, 2H), 6.52(d, *J*=4.8Hz, 1H), 5.24(s, 2H), 3.56(s, 3H); ESMS calcd for C₁₈H₁₄N₂O₃: 306.10; Found: 307.1 (M+H)⁺.

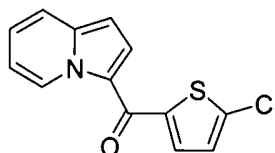
Example 16: Indolizin-3-yl-(4-nitro-phenyl)-methanone



10

¹H-NMR (CDCl₃) δ (ppm), 9.97(d, *J*=6.6Hz, 1H), 8.33(d, *J*=6.9Hz, 2H), 7.92(d, *J*=6.9Hz, 2H), 7.61(d, *J*=8.7Hz, 1H), 7.30-7.25(m, 2H), 7.01(t, *J*=6.6Hz, 1H), 6.57(d, *J*=3.0Hz, 1H); ESMS calcd for C₁₅H₁₀N₂O₃: 266.07; Found: 267.0 (M+H)⁺.

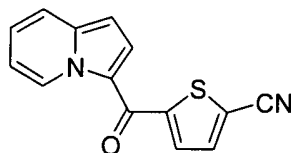
Example 17: (5-Chloro-thiophen-2-yl)-indolizin-3-yl-methanone



15

¹H-NMR (CDCl₃) δ (ppm), 9.79(d, *J*=7.2Hz, 1H), 7.61(d, *J*=4.5Hz, 1H), 7.55-7.50(m, 2H), 7.15(t, *J*=7.5Hz, 1H), 6.95(d, *J*=3.9Hz, 1H), 6.88(t, *J*=7.2Hz, 1H), 6.53(d, *J*=4.8Hz, 1H); ESMS calcd for C₁₃H₈ClNOS: 261.00; Found: 262.0 (M+H)⁺.

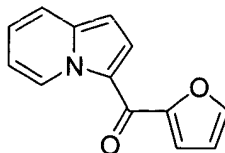
Example 18: 5-(Indolizine-3-carbonyl)-thiophene-2-carbonitrile



20

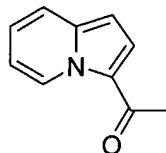
¹H-NMR (CDCl₃) δ (ppm), 9.88(d, *J*=6.9Hz, 1H), 7.68-7.63(m,4H), 7.30-7.25(m, 1H), 7.00(t, *J*=6.9Hz, 1H), 6.61(d, *J*=4.5Hz, 1H); ESMS calcd for C₁₄H₈N₂OS: 252.04; Found: 253.0 (M+H)⁺.

Example 19: Furan-2-yl-indolizin-3-yl-methanone



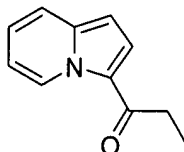
¹H-NMR (CDCl₃) δ (ppm), 10.01(d, *J*=7.2Hz, 1H), 8.05(d, *J*=4.5Hz, 1H), 7.63(s,1H), 7.56(d, *J*=8.7Hz, 1H), 7.29-7.27m,1H), 7.17(t, *J*=6.9Hz, 1H),6.91(t, *J*=6.9Hz, 1H), 6.60-6.56(m, 2H); ESMS calcd for C₁₃H₉NO₂: 211.06; Found: 212.1 (M+H)⁺.

Example 20: 1-Indolizin-3-yl-ethanone



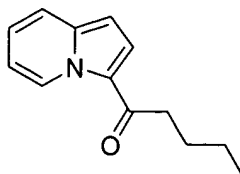
¹H-NMR (CDCl₃) δ (ppm), 9.84 (d, *J*=8.1, 1H), 7.47 (m, 2H), 7.07 (t, *J*=6.8, 1H), 6.82 (t, *J*=6.8, 1H), 6.47 (d, *J*=5.9, 1H), 2.54 (s, 3H). ESMS calcd for C₁₀H₉NO: 159.07; Found: 160.1 (M+H)⁺.

Example 21: 1-Indolizin-3-yl-propan-1-one



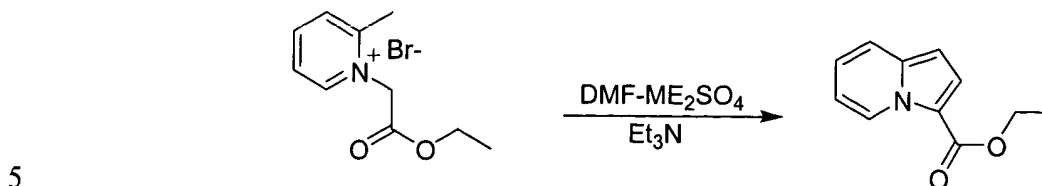
¹H-NMR (CDCl₃) δ (ppm), 9.89 (d, *J*=7.7, 1H), 7.49 (d, *J*=6.0, 2H), 7.08 (t, *J*=6.7, 1H), 6.82 (t, *J*=6.7, 1H), 6.47 (d, *J*=4.1, 1H), 2.91 (dd, *J*=10.1, 2H), 1.27 (t, *J*=10.1, 3H). ESMS calcd for C₁₁H₁₁NO: 173.08; Found: 174.1 (M+H)⁺.

Example 22: 1-Indolizin-3-yl-pentan-1-one



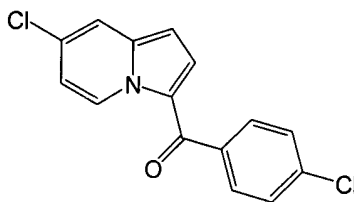
^1H -NMR (CDCl_3) δ (ppm), 9.88 (d, $J=7.2$, 1H), 7.51 (d, $J=6.4$, 2H), 7.13 (t, $J=6.8$, 1H), 6.82 (t, $J=4.8$, 1H), 6.48 (d, $J=3.8$, 1H), 2.83 (t, $J=10.2$, 2H), 1.76-1.42 (m, 4H), 0.94 (t, $J=9.8$, 3H). ESMS calcd for $\text{C}_{13}\text{H}_{15}\text{NO}$: 201.12; Found: 202.1 ($\text{M}+\text{H}$) $^+$.

Example 23: Indolizine-3-yl-phenyl-methanone



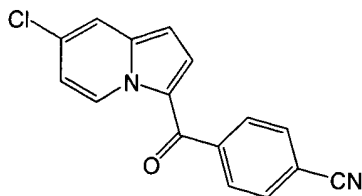
^1H NMR (300 MHz, CDCl_3), δ (ppm): 9.43 (dd, $J = 7.2$ Hz, 0.6 Hz, 1H); 7.47-7.53 (m, 2H); 7.00 (m, 1H); 6.79 (m, 1H); 6.48 (d, $J = 3.9$ Hz, 1H); 4.38 (q, $J = 7.2$ Hz, 2H); 1.40 (t, $J = 7.2$ Hz, 3H); 11% yield; ESMS calcd. for $\text{C}_{11}\text{H}_{12}\text{NO}_2$ ($\text{M} + \text{H}$) $^+$: 190.1; Found: 190.1.

10 **Example 24: (7-Chloro-indolizin-3-yl)-(4-chloro-phenyl)-methanone**



15 ^1H NMR (300 MHz, CDCl_3), δ (ppm): 9.85 (d, $J = 7.5$ Hz, 1H); 7.73-7.75 (m, 2H); 7.55-7.56 (m, 1H); 7.45-7.48 (m, 2H); 7.32 (d, $J = 7.5$ Hz, 1H); 6.91 (dd, $J = 7.5$ Hz, 1.5 Hz, 1H); 6.49 (d, $J = 4.8$ Hz, 1H); ESMS calcd. for $\text{C}_{15}\text{H}_{10}\text{Cl}_2\text{NO}$ ($\text{M} + \text{H}$) $^+$: 290.1; Found: 290.1.

Example 25: (7-Chloro-indolizin-3-yl)-(4-cyano-phenyl)-methanone



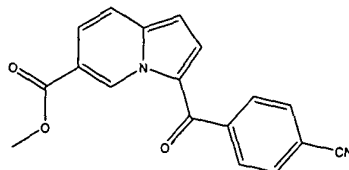
20 ^1H NMR (300 MHz, CDCl_3), δ (ppm): 9.88 (d, $J = 7.5$ Hz, 1H); 7.78-7.88 (m, 4H); 7.59 (dd, $J = 7.5$ Hz, 0.9 Hz, 1H); 7.26-7.28 (m, 1H); 6.96 (dd, $J = 7.5$ Hz, 2.4 Hz, 1H);

6.52 (dd, $J = 7.5$ Hz, 0.6 Hz, 1H); ESMS calcd. for $C_{16}H_{10}ClN_2O$ ($M + H$)⁺: 281.0;

Found: 281.0.

Example 26: 3-(4-cyano-benzoyl)-indolizine-6-carboxylic acid methyl ester

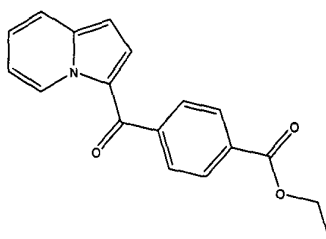
5



¹H-NMR ($CDCl_3$) δ (ppm), 10.60(s, 1H), 7.92-7.89(m, 2H), 7.82-7.77(m, 3H), 7.62(d, $J=9.6$ Hz, 1H), 7.38(d, $J=6.3$ Hz, 1H), 6.63(d, $J=4.5$ Hz, 1H), 3.99(s, 3H); ESMS clcd for $C_{18}H_{12}N_2O_3$: 304.08; Found: 305.1 ($M+H$)⁺.

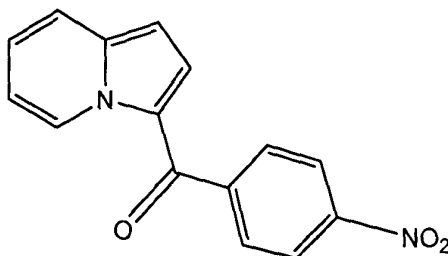
10

Example 27: 4-(indolizine-3-carbonyl)-benzoic acid ethyl ester



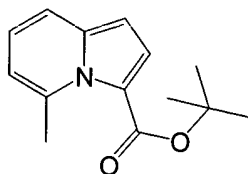
¹H-NMR ($CDCl_3$) δ (ppm), 9.98(d, $J=6.6$ Hz, 1H), 8.17-8.14(m, 2H), 7.85-7.82(m, 2H), 7.59(d, $J=9.3$ Hz, 1H), 7.30-7.20(m, 2H), 6.97(t, $J=7.2$ Hz, 1H), 6.54(d, $J=4.8$ Hz, 1H), 4.42(q, $J=6.9$ Hz, $J=15$ Hz, 2H), 1.43(t, $J=7.2$ Hz, 3H); ESMS clcd for $C_{18}H_{15}NO_3$: 293.11; Found: 294.2 ($M+H$)⁺.

Example 28: Indolizin-3-yl-(4-nitro-phenyl)-methanone



$^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ 6.5 (m, 1H), 6.7 (m, 1H), 6.8 (d, 1H, $J=5$), 7.4 (d, 1H, $J=5$), 7.8 (d, 1H, $J=5$), 8.0 (d, 1H, $J=5$), 8.3 (d, 2H, $J=8$), 8.6 (d, 1H, $J=8$) ppm. ESMS calcd for $\text{C}_{15}\text{H}_{10}\text{N}_2\text{O}_3$: 266.1; Found: 267.1 ($\text{M}+\text{H}$) $^+$.

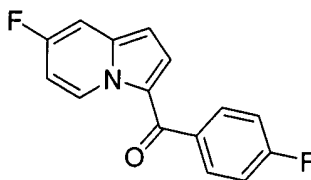
Example 29: 5-Methyl-indolizine-3-carboxylic acid tert-butyl ester



5

$^1\text{H-NMR}$ (CDCl_3) δ 1.5 (s, 9H), 2.6 (s, 3H), 6.4 (d, 1H, $J=4$), 6.5 (d, 1H, $J=8$), 6.9 (dd, 1H, $J=8, 8$), 7.3 (d, 1H, $J=8$), 7.4 (d, 1H, $J=5$) ppm. ESMS calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2$: 231.1; Found: 232.1 ($\text{M}+\text{H}$) $^+$.

Example 30: (7-Fluoro-indolizin-3-yl)-(4-fluorophenyl)-methanone

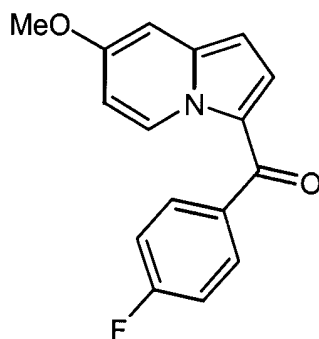


10

$^1\text{H NMR}$ δ ($\text{DMSO-}d_6$) 9.96 (dd, $J_1=5.4$ Hz, $J_2=7.8$ Hz, 1H), 7.81 (dd, $J_1=8.7$ Hz, $J_2=5.4$ Hz, 2H), 7.34 (d, $J=4.5$ Hz, 1H), 7.14-7.20 (m, 2H), 6.49-6.81 (m, 3H), 6.48 (d, $J=4.8$ Hz, 1H); ESMS Calcd ($\text{C}_{15}\text{H}_9\text{F}_2\text{NO}$): 257.07, found 258.1 ($\text{M}+\text{H}$) $^+$.

15

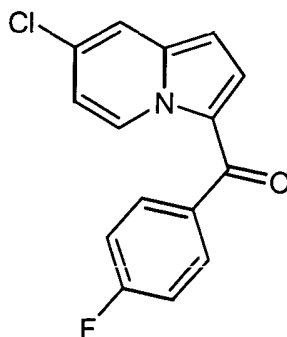
Example 31: (4-Fluoro-phenyl)-(7-methoxy-indolizin-3-yl)-methanone



$^1\text{H-NMR}$ (CDCl_3 , 300MHz): δ 9.83 (d, $J=7.8$ Hz, 1H), 7.82-7.77 (m, 2H), 7.25 (d, $J=4.5$ Hz, 1H), 7.17-7.12 (m, 2H), 6.82 (d, $J=2.4$ Hz, 1H), 6.65 (dd, $J=2.4, 7.8$ Hz,

1H), 6.34 (d, $J = 4.5\text{Hz}$, 1H), 3.89 (s, 3H, OCH_3); ES-MS: Calculated: $\text{C}_{16}\text{H}_{12}\text{FNO}_2$: 269.09, Found: 270.0 ($\text{M}+\text{H}$)⁺.

Example 32: (7-Chloro-indolizin-3-yl)-(4-fluoro-phenyl)-methanone

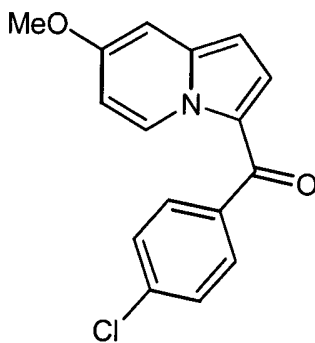


5

¹H-NMR (CDCl_3 , 300MHz): δ 9.85 (dt, $J = 0.6, 7.2\text{Hz}$, 1H), 7.84-7.79 (m, 2H), 7.56 (dd, $J = 0.6, 2.4\text{Hz}$, 1H), 7.33 (d, $J = 4.5\text{Hz}$, 1H), 7.20-7.14 (m, 2H), 6.90 (dd, $J = 2.1, 7.8\text{Hz}$, 1H), 6.49 (d, $J = 4.5\text{Hz}$, 1H); ES-MS: Calculated: $\text{C}_{15}\text{H}_9\text{ClFNO}$: 273.04, Found: 274.0 ($\text{M}+\text{H}$)⁺.

10

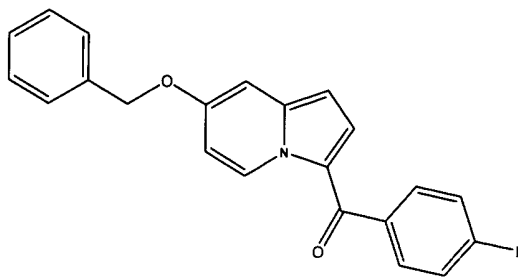
Example 33: (4-Chloro-phenyl)-(7-methoxy-indolizin-3-yl)-methanone



¹H-NMR (CDCl_3 , 300MHz): δ 9.85 (d, $J = 7.8\text{Hz}$, 1H), 7.74-7.71 (m, 2H), 7.46-7.42 (m, 2H), 7.24 (d, $J = 4.2\text{Hz}$, 1H), 6.83 (d, $J = 2.4\text{Hz}$, 1H), 6.66 (dd, $J = 2.7, 7.8\text{Hz}$, 1H), 6.35 (d, $J = 4.8\text{Hz}$, 1H), 3.89 (s, 3H); ES-MS: Calculated: $\text{C}_{16}\text{H}_{12}\text{ClINO}_2$: 285.06, Found: 286.0 ($\text{M}+\text{H}$)⁺.

15

Example 34: (4-Chloro-phenyl)-(7-methoxy-indolizin-3-yl)-methanone



(7-Benzyloxy-indolizin-3-yl)-(4-fluoro-phenyl)-methanone

$^1\text{H-NMR}$ (CDCl_3) δ (ppm), 9.82 (d, , $J=12$, 1H), 7.79-6.65(m, 12H), 6.32(d, J
5 =5, 1H), 5.14 (s, 2H). ESMS clcd for $\text{C}_{22}\text{H}_{16}\text{FNO}_2$: 345.12; Found: 346.2 ($\text{M}+\text{H}$) $^+$.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.